



Sudden cardiac death caused by hypertrophic cardiomyopathy associated with midventricular obstruction and apical aneurysm

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Heart 2003;89:178-
doi:10.1136/heart.89.2.178

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CARDIOVASCULAR MEDICINE

Rarefaction of skin capillaries in normotensive offspring of individuals with essential hypertension

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Heart 2003;89:175–178

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Accepted 18 September
2002

Background: Rarefaction of skin capillaries in people with intermittent borderline essential hypertension suggests a primary or an early abnormality that may antedate the onset of sustained hypertension.

Objective: To compare skin capillary density in subjects with and without a family history of essential hypertension.

Subjects: 21 normotensive individuals, one or both of whose parents had essential hypertension (mean age 39.3 years; blood pressure 124/79 mm Hg); 21 normotensive controls with no family history of hypertension (age 46.3 years; blood pressure 124/78 mm Hg).

Methods: The skin of the dorsum of the fingers was examined by intravital capillary microscopy before and after venous congestion at 60 mm Hg for two minutes.

Results: By analysis of variance, both baseline and maximum skin capillary density were lower in subjects with a family history of essential hypertension than in those with no family history (baseline: 67 v 79 capillaries per field, $p = 0.008$; maximum: 74 v 93 capillaries per field, $p < 0.0005$).

Conclusions: Capillary rarefaction in essential hypertension may occur before the increase in blood pressure and could, at least in part, reflect a primary rather than a secondary abnormality.

There is increasing interest in structural and functional abnormalities of the microcirculation in cardiovascular disease and in particular in essential hypertension.¹ A reduction in the density (rarefaction) of capillaries and arterioles is a consistent finding in many tissues in human essential hypertension.^{2,3} Several experimental animal studies have suggested that microvascular rarefaction—especially of small arteries and arterioles—contributes to the increase in vascular resistance in hypertension^{4–6} and may affect muscle perfusion and metabolism.⁷ It was recently shown that rarefaction of capillaries of the skin of the dorsum of fingers in essential hypertension is likely to be caused mainly by the structural (anatomical) absence of capillaries rather than by functional non-perfusion.⁸ We have also shown that individuals with intermittent borderline essential hypertension have a skin capillary density that is as low as or even lower than in individuals with established hypertension, suggesting that rarefaction may be an early abnormality in essential hypertension rather than a result of the sustained elevation of blood pressure.⁹

To try to establish whether microvascular rarefaction occurs before the blood pressure becomes abnormal, we investigated normotensive offspring of patients with essential hypertension to determine whether they also have rarefaction of their skin capillaries.

METHODS

Subjects

Twenty one normotensive individuals with a family history of essential hypertension in one or both parents were enrolled in the study. They were recruited from the offspring of patients attending the blood pressure unit at St George's Hospital. We also studied 21 healthy normotensive individuals who had no family history of hypertension and who were closely matched for systolic and diastolic blood pressures. These individuals were recruited by local posters and by announcements in the national media.

A standard questionnaire was used to obtain information about current and previous smoking habits, a history of hypertension and diabetes mellitus, and a family history of hypertension, coronary artery disease, and strokes. Individuals with a history of connective tissue disease, diabetes mellitus, and skin diseases, and any who were on vasoactive drugs were excluded from the study. Those with cold hands or Raynaud's phenomenon were also excluded.

The protocol was approved by the local research ethics committee of St George's Hospital. Written informed consent was obtained from each subject.

Intravital capillaroscopy

Intravital microscopy was carried out using a standardised well validated technique.¹⁰ Individuals were studied in the morning between 9 am and 11 am after an overnight fast. The capillaroscopy studies were done in a temperature controlled laboratory (21–24°C) after the subjects had had at least 20 minutes of semisupine rest. Room temperature was monitored before and during the studies and if necessary was adjusted using fan heaters or air conditioning. Subjects were seated with the left forearm and hand supported at heart level. Movement of the hand and the forearm was restricted by resting them on a splint surrounded by a vacuum pillow (a specially constructed pillow filled with polyurethane foam that can be moulded to any desired shape by creating a vacuum). We used video microscopy with an epi-illuminated microscope containing a 100 W mercury vapour lamp light source and a PL 6.3/0.2 objective (Wild-Leitz type 307-143.004, Leica UK), final magnification $\times 196$. Microscopic images were obtained with a CCD camera (Hitachi, model CCD HV-725K) and transferred using a video scaler (VS-1000) and a video timer (For-A VTG 33) for storage onto a video recorder (Panasonic model AUC 7350). The skin of the dorsum of the middle phalanx of the non-dominant hand was examined. Four microscopic fields (0.68 mm² each) around a central ink spot were recorded continuously for five minutes so as to detect intermittently perfused capillaries. Multiple still frame

video prints (Sony multiscan video printer, UP-930) obtained from each recorded field were analysed off-line. A transparent acetate sheet was placed over these prints and the capillaries were traced. The same acetate sheet was then used with the video monitor during live playback of the recorded tapes. Additional intermittently perfused capillaries which were not visible on the initial still frame images could then be marked on the acetate sheet. The total number of visible capillaries was counted by hand from these acetate sheets.

For each studied subject, five acetate sheets were obtained for analysis, one from each of four different fields at baseline and one during venous congestion. The analysis of each capillaroscopy study lasted around three hours. Capillary density was analysed twice by two investigators (TFTA and FMR) in a blinded fashion. The clinical characteristics and particulars of the family history of the study subjects were not available to either investigator during capillary counting.

Reproducibility was first assessed by examining an identical area of skin marked by a microtattoo (by implanting a drop of sterile methylene blue ink into the epidermis with a 23 gauge hypodermic needle) to act as a reference point. Intraobserver repeatability of data analysis was assessed by reading the same prints in a blinded manner on two separate occasions ($n = 20$; coefficient of variability 4.3%). To assess interobserver repeatability, a second observer independently assessed capillary density in the same prints ($n = 20$; coefficient of variability 5.9%). Skin temperature was monitored throughout the study with a temperature probe on the dorsum of the left index finger (YSI Tele-Thermometers).

Maximisation of visualised skin capillaries

We have recently shown that venous congestion maximises the number of visible capillaries much more than reactive hyperaemia.¹⁰ In this study a miniature blood pressure cuff was applied to the base of the left middle finger and the cuff was then inflated and maintained at 60 mm Hg for two

minutes; further images were then recorded using one of the four microscopic fields chosen at random.

Blood pressure and heart rate

Blood pressure was measured with an automatic oscillometric device (Omron HEM705CP, Omron Healthcare, Henfield, West Sussex, UK) with appropriate cuff size. Supine and standing blood pressure measurements were taken as the mean of three readings obtained at one to two minute intervals with the individual in the corresponding position.

Blood and urine analysis

Venous blood was taken without stasis after the patient had been sitting upright for 10 minutes. Variables measured included serum electrolytes, urea, creatinine, uric acid, glucose, total cholesterol, triglycerides, and full blood count.

Statistical analysis

All results are given as mean (SEM). The data were processed by StatView 5.0 (SAS Institute Inc, Cary, North Carolina, USA). Analysis of variance (ANOVA) and Bonferroni's post hoc tests were used to compare the groups.

RESULTS

Table 1 shows baseline clinical and laboratory characteristics and capillaroscopic data at baseline and after two minutes of venous congestion at 60 mm Hg in the study individuals. As the index and control subjects were matched for blood pressure, it was necessary to recruit slightly older individuals in the control group (39.3 (2.8) v 46.3 (2.1) years, $p = 0.052$ by ANOVA), because people with a family history of hypertension have higher blood pressures (albeit in the normal range) than age and weight matched people with no family history of hypertension.

There was a significant (15%) lower mean capillary density in the index subjects at baseline than in the controls (67 (2) v 79 (4) capillaries per field (0.68 mm²); $p = 0.008$). After two minutes of venous congestion, maximum capillary density remained significantly lower (by 20%) in the index group than in the controls (74 (2) v 93 (4) capillaries per field (0.68 mm²); $p = 0.0005$) (fig 1).

Table 1 Baseline characteristics and capillaroscopic data of 21 normotensive subjects with a parental history of essential hypertension and 21 healthy normotensive controls with no family history of hypertension

	Parental history (n=21)	No parental history (n=21)
Age (years)	39.3 (2.8)	46.3 (2.1)
Weight (kg)	78.4 (3.9)	77.1 (2.6)
Height (cm)	171.7 (2.2)	173.0 (1.9)
BMI (kg/m ²)	26.5 (1.2)	25.7 (0.7)
Blood pressure (mm Hg)		
Supine	124/79 (3/2)	124/78 (2/1)
Standing	127/83 (3/2)	121/81 (2/1)
Pulse rate (beats/min)		
Supine	70 (4)	69 (2)
Standing	75 (3)	74 (2)
Haematology		
Haemoglobin (g/dl)	14.5 (0.3)	14.3 (0.2)
PCV	0.421 (0.01)	0.421 (0.01)
Platelets	225 (11.4)	222 (13)
Biochemistry		
Sodium (mmol/l)	139 (0.4)	140 (0.4)
Potassium (mmol/l)	4.4 (0.08)	4.1 (0.05)
Urea (mmol/l)	4.6 (0.3)	5.1 (0.3)
Creatinine (μmol/l)	74.7 (3.6)	88.7 (2.5)
Glucose (mmol/l)	5.1 (0.1)	5.0 (0.1)
Cholesterol (mmol/l)	5.2 (0.2)	5.2 (0.1)
Triglycerides (mmol/l)	1.3 (0.1)	1.0 (0.2)
Mean capillary density/field (0.68 mm ²)		
At baseline	67 (2)*	79 (4)
With venous congestion	74 (2)**	93 (4)

Values are mean (SEM).

* $p < 0.01$; ** $p < 0.001$ by analysis of variance.

PCV, packed cell volume.

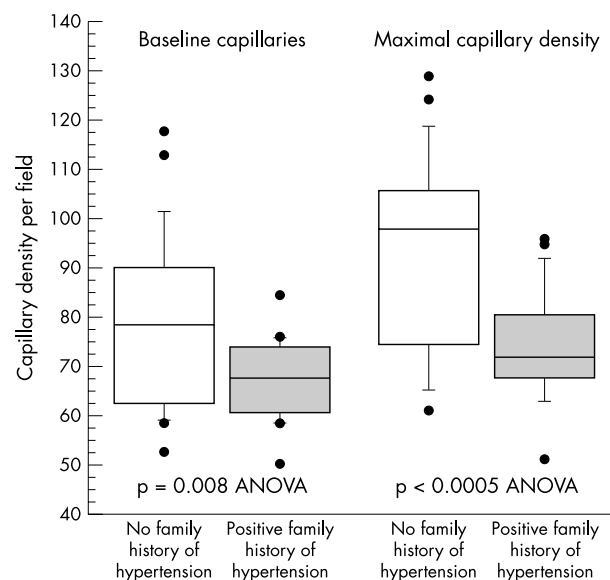


Figure 1 Box plot showing skin capillary density before and after venous congestion in 21 normotensive individuals with a family history of essential hypertension in one or both parents and in 21 normotensive controls with no family history of hypertension. The graph shows the 10th, 25th, 50th (median), 75th, and 90th centiles of the data.

DISCUSSION

Our major finding in this study was that normotensive subjects whose parents have essential hypertension have rarefaction of their skin capillaries. This reduction in capillary density in comparison with controls with no family history of hypertension was of similar degree before and after maximisation of capillary visibility. This suggests that the rarefaction is likely to reflect the structural absence of capillaries rather than a functional abnormality. This does not, of course, rule out the presence of additional functional abnormalities in the microcirculation. As essential hypertension is, at least in part, an inherited condition, our results indicate that capillary rarefaction occurs early in essential hypertension independently of the blood pressure (that is, it is a primary structural abnormality), or that it is associated with whatever eventually causes the rise in blood pressure. It is doubtful whether the skin circulation plays an important role in blood pressure regulation. However, it is widely believed that capillary rarefaction in essential hypertension is not limited to the skin but is a more generalised abnormality that affects different vascular beds.^{11–13}

Our results are in agreement with previous studies that reported structural abnormalities of the vasculature in normotensive individuals with a parental history of essential hypertension. Noon and colleagues reported that offspring with raised blood pressure whose parents also had a high blood pressure had fewer capillaries on the dorsum of their fingers than those whose parents had a lower blood pressure.¹⁴ However, as blood pressure was raised in these individuals, a secondary decrease in capillary density cannot be excluded. In our study, the index and control groups were carefully matched for both systolic and diastolic blood pressure, thus excluding the possibility of a secondary effect of a higher blood pressure on capillary density. However, because of blood pressure matching, the mean age of our control group (the individuals without a family history of hypertension) was slightly higher than the group with the family history. Other studies^{15–16} have previously shown that individuals with a family history of hypertension have higher blood pressures (albeit in the normal range) than their age and weight matched peers with no family history of hypertension. Previous work has also suggested that aging is associated with a significant reduction in skin capillary density and rarefaction of the larger microvessels.^{17–19} It seems very unlikely that the small difference in age between our two groups would have made any significant impact on our results. However, the slightly older control group would in no way weaken our results but would rather tend to reinforce them, as the difference in capillary density may have been underestimated.

There is now increasing evidence that both structural and functional abnormalities of the vasculature are present at an early stage in normotensive individuals with a parental history not only of essential hypertension but also of other cardiovascular diseases.^{20–21} Abnormalities have been described in larger conduit arteries, such as increased arterial stiffness, as well as in smaller resistance arteries and arterioles. Meaney and colleagues found that children and adolescents with a parental history of hypertension had greater carotid stiffness and smaller carotid diameters than the offspring of normotensive parents.²² Takeshita and colleagues examined maximum vasodilator capacity of forearm resistance vessels in normotensive young men with hypertensive relatives and in normotensive controls with no family history of hypertension.²³ They found that minimum forearm vascular resistance was 25% higher in subjects with hypertensive relatives than in subjects with no family history. They suggested that there might be a structural abnormality in the forearm resistance vessels in normotensive subjects with a family history of hypertension. Our finding of approximately 20% lower microvascular density in normotensive individuals with a family history of hypertension provides a possible explanation for Takeshita's results.

Other abnormalities that have been described in normotensive individuals with a familial predisposition to hypertension include insulin resistance, increased sympathetic activity, and raised adrenaline and endothelin concentrations.^{24–27} Recently Zizek and colleagues have shown that flow mediated vasodilatation in response to reactive hyperaemia was significantly lower in normotensive young subjects who had a family history of essential hypertension than in the offspring of normotensive parents.²⁰ Similar findings were also reported in normotensive offspring of patients with premature myocardial infarction who were found to have a lower flow mediated reactivity of the brachial arteries and a greater mean intima-media thickness of the common carotid artery.²¹

Conclusions

Our study shows significantly lower skin capillary density in healthy normotensive individuals with a familial predisposition to essential hypertension. The clinical significance of capillary rarefaction in the normotensive offspring of hypertensive parents remains unknown. Further studies are needed to determine any possible correlation between capillary rarefaction and the haemodynamic or metabolic abnormalities that have been described in this group of individuals. Primary structural rarefaction of capillaries may support the hypothesis of reduced microvascular growth in primary hypertension. This implies that capillary rarefaction in this setting does not represent a secondary disappearance of blood vessels, but reflects a decreased angiogenic capacity of the microcirculation of individuals predisposed to hypertension. This reduction in vascular growth may affect different organs and be expressed in divergent ways in distinct phenotypes of the cardiovascular risk syndrome.²⁸

ACKNOWLEDGEMENTS

This research was supported by the British Heart Foundation.

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IMAGES IN CARDIOLOGY.....

Sudden cardiac death caused by hypertrophic cardiomyopathy associated with midventricular obstruction and apical aneurysm

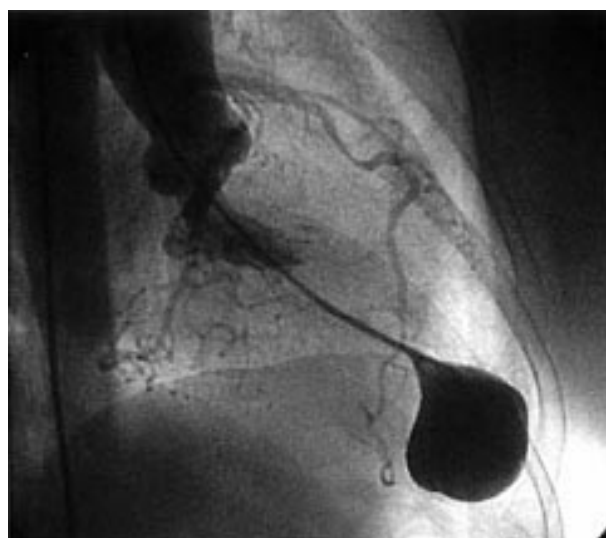
A 79 year old woman with a history of good health presented with sudden cardiac arrest caused by ventricular fibrillation. She was successfully resuscitated and admitted into the coronary care unit. An ECG showed sinus rhythm with left ventricular hypertrophy with T wave inversion over V4–V6. Serial cardiac enzymes were normal. An echocardiogram showed asymmetric septal hypertrophy, midventricular obstruction, and an apical aneurysm. Cardiac catheterisation showed angiographically normal coronary arteries. Left ventriculogram revealed severe left ventricular hypertrophy with systolic midventricular total obstruction and apical aneurysm (below

left and right). A peak-to-peak intraventricular pressure gradient of 110 mm Hg was documented during pullback from the apical high pressure chamber (270 mm Hg) to the subaortic low pressure chamber in the left ventricle (160 mm Hg). The patient was subsequently treated with a β blocker and an implantable cardioverter-defibrillator was implanted.

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Left ventriculogram in right anterior oblique (30°) projection during systole showing nearly complete midventricular obstruction with apical aneurysm.



Left ventriculogram in right anterior oblique (30°) projection during diastole showing severe midventricular hypertrophy with apical aneurysm.